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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/528,923
Filing Date: March 23, 2005
Appellant(s): NAKAS ET AL.

David E. Rook
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4/15/09 appealing from the Office action mailed 1/16/09.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is substantially correct but incomplete as it fails to indicate that the claims were amended with the filing of the instant brief to correct the inadvertent error introduced into the claims during the after-final amendment of March 27, 2008. This amendment will be entered as it overcomes the 112, 2nd rejection presented on pages 3-4 of the Final Rejection which applied to claims 1, 3-7, 9 and 18. It should be noted that the 112, 2nd rejection presented on

pages 4-5 of the Final Rejection which applied to claim 9 only is not overcome.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner: the 112, 2nd rejection presented on pages 3-4 of the Final Rejection which applied to claims 1, 3-7, 9 and 18.

GROUNDS OF REJECTION NOT ON REVIEW

The following grounds of rejection have not been withdrawn by the examiner, but they are not under review on appeal because they have not been presented for review in the appellant's brief: the 112, 2nd rejection presented on pages 4-5 of the Final Rejection which applied to claim 9 only.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

J. L. Bertrand et al., "Biosynthesis of Poly-β-Hydroxyalkanoates from Pentoses by Psuedomonas pseudoflava," Applied and Enviromental Microbiology, 56(10): 3133-3138, (Oct. 1990).

S.H. Chung et al., "Effect of Levulinic Acid on the Production of Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) by *Ralstonia eutropha* KHB-8862" Journal of Microbiology 39(1): 79-82 (March 2001).

J.H. Jang et al., "Effect of Levulinlc Acid on Cell Growth and Poly-β-Hydroxyalkanoate Production by *Alcaligenes* sp. SH-69" Biotechnology Letters, 18(2): 219-224 (1996).

S.Y. Lee, "Poly(3-hydroxybutyrate) Production from Xylose by Recombinant *Escherichia coli*" Bioprocess Engineering, 18: 397-399 (1998).

J.A. Ramsay et al., "Hemicellulose as a Potential Substrate for Production of poly(β-hydroxyalkanoates)" Can. J. Microbiol., 41(Suppl.1): 262-266 (1995).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 3-7, 9 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Lee, Ramsay et al., Bertrand et al., Chung et al. and Jang et al. (all cited on the IDS of 9/16/05).

Each of Lee, Ramsay et al. and Bertrand et al. teach the production of the polyhydroxyalkanoate PHB with a microorganism using the sugar xylose as the main carbon source. Each of Ramsay et al. and Bertrand et al. specifically derived the

xylose used for the PHB production from a hemicellulose hydrosylate. None of Lee, Ramsay et al. and Bertrand et al. used levulinic acid as a cosubstrate for the production of P(3HB-co-3HV).

Each of Chung et al. and Jang et al. teach the production of the polyhydroxyalkanoate P(3HB-co-3HV) with a microorganism using glucose as a primary carbon source and levulinic acid as a secondary carbon source. Chung et al. used ratios of levulinic acid/glucose of 0-0.2 while Jang et al. used ratios of 0-0.1. They teach that P(3HB-co-3HV) is a particularly useful PHA having a range of desirable thermomechanical properties of interest and that levulinic acid is cheaper and more effectively utilized as a cosubstrate for production of P(3HB-co-3HV) than other known cosubstrates. Chung et al. also teach addition of additional amounts of levulinic acid to the culture after an period of several hours in order to maintain the level of LA in the culture at a constant amount and Jang et al. and Chung et al. teach that the ratio of HV to HB can be modulated by adjusting the ratio of the primary and secondary carbon sources, i.e., increased amounts of HV in the copolymer are produced by increased amounts of the cosubstrate. Furthermore, Jang et al. teach that low levels of levulinic acid addition (i.e., 0.5 g/L)

was very effective for stimulating cell growth as well as for copolymer accumulation (see page 222).

The skilled artisan is well aware that PHA accumulation in most microorganisms does not occur linearly during the growth phase but occurs only after nitrogen depletion of media begins (see Figure 2 of Bertrand and Fig 1 of Ramsey et al.) and that cosubstrates used to produce the HV unit of P(3HB-co-3HV) are often growth inhibitory at high concentrations. As such many P(3HB-co-3HV) cultivations are done as two stage cultivations including an initial growth phase on the primary substrate followed by addition of the cosubstrate at the time of nitrogen depletion and PHA accumulation. However, as Jang et al. teach that low levels of levulinic acid are actually growth stimulatory and as Lee, Ramsay et al. and Bertrand et al. all teach that xylose is a much cheaper primary carbon souse for PHB production, it would have been obvious to add low amounts of levulinic acid to the cultures of the microorganisms of any of Lee, Ramsay et al. and Bertrand et al. at the beginning of the culture and to add a larger amount of levulinic acid as a cosubstrate at the time of nitrogen depletion (at approximately 16-30 hrs in the cultures of Bertrand et al. and Ramsey et al., see Figure 2 of Bertrand and Fig 1 of Ramsey et al.) in order to

produce P(3HB-co-3HV) in these microorganisms from the cheaper primary carbon source xylose.

(10) Response to Argument

Appellants assert that no convincing line of reasoning from the five references cited to Appellant's invention has been presented by the Office. Appellants assert that it would not have been obvious at the time of the invention, to have modified and combined the five references as suggested by the Office but that, absent appellants teachings, the Office's rejection is legally and logically untenable. However, this is not persuasive as it is the examiners position that clear reasons have been presented for all of the conclusions of the rejection. The rejection clearly presents reasons for using xylose as the primary carbon source (xylose is cheaper than other possible primary carbon sources), for using levulinic acid as the secondary carbon source (production of the more desirable polymer P(3HB-co-3HV) requires the presence of a cosubstrate and levulinic acid is cheaper and more effectively utilized as a cosubstrate for production of P(3HB-co-3HV) than other known cosubstrates) and for adding a small amount of the levulinic acid at the beginning of the fermentation (small amounts of levulinic acid are growth stimulatory) and a larger amount at about 16-24 hours later (this is the time point at which PHA

synthesis begins and at this point the amount of the 3HV incorporated into the polymer is related to the amount of levulinic acid present so larger amounts are needed to get a reasonable amount of HV present in the P(3HB-co-3HV) polymer). Furthermore, the rejection clearly points out where in the references themselves these reasons are taught and thus the rejection does not in fact use the appellants teaching to support the rejection.

Appellants argue that the limitation that a second, larger quantity of levulinic acid is added between about 16 hours and about 24 hours after the addition of a first, smaller quantity of levulinic acid is non-obvious and that none of the cited references teaches or suggests a second, larger addition of levulinic acid. However, this is not persuasive as the rejection explains why a skilled artisan would have found this obvious. As discussed in the rejection the disclosure of Jang et al. teaches that low levels of levulinic acid (LA) are growth stimulatory while both Jang et al. and Chung et al. teach that high levels of LA increase the mol % of HV in the copolymer but are growth inhibitory. A skilled artisan which is attempting to produce high levels of the P(3HB-co-3HV) copolymer would use growth stimulatory amounts of levulinic acid during the growth phase (before PHA production begins) in order to achieve the

highest possible level of microorganism in the culture prior to the introduction of a growth inhibitory substance (i.e. the levels of levulinic acid necessary for sufficient HV incorporation to occur) and then to add additional higher levels of LA as necessary for copolymer production at the time of nitrogen depletion in order to provide to for production of the P(3HB-co-3HV) copolymer with sufficient levels of the HV momomer. As such while the references do not explicitly suggest the limitation of the claims the teaching of the cited references in combination with the knowledge of the skilled artisan would have suggested this method.

Appellants argue that Bertrand et. al teaches the addition of propionic acid (PA) as a secondary carbon source but does not teach a two-stage addition of the secondary carbon source with the second addition being in a quantity greater than the first. Lee and Ramsay et al. do not teach the addition of a secondary carbon source at all, Jang et al. teaches the addition of LA as a secondary carbon source but does not teach the subsequent addition of LA to the culture after the first addition of LA. and Chung et al. teaches the use of LA as a secondary carbon source and teaches the use of additional amounts of LA to maintain the level of LA in the culture at a constant amount and thus none of the references teach the addition of a first and

second quantity of a secondary carbon source with the second quantity being greater than the first quantity. While this is a true statement it is noted that the instant rejection is made under 103 and not under 102 and includes a well reasoned explanation as to why a skilled artisan given the disclosure of all of these references would have found it obvious to do just this. Merely because none of the references did so or explicitly suggested doing so is not evidence that the combined disclosures do not in fact suggest what is claimed. The rationale advanced in the instant rejection is clearly based on the various facts provided by the cited references and NOT on facts disclosed by applicants and thus does provide a *prima facie* case of obviousness.

Appellants argue that neither Chung et al. nor Jang et al. teach or suggest the use of xylose as a primary carbon source. This is noted but appellants are reminded that the rejection was not made over only the Chung et al. and Jang et al. references but over the combination of these references with Lee, Ramsay et al. and Bertrand et al. Each of these three references teach the use of xylose as the primary carbon source for PHB production and why (i.e., cheaper cost of xylose) a skilled artisan would select xylose as primary carbon source instead of glucose as used by Chung et al. and Jang et al. As such the

combination of reference cited by the examiner does suggest the use of xylose as the primary carbon source.

Appellants argue that none of the cited references provides the suggestion or motivation to combine or modify the teachings of any other cited reference and the Office fails to provide any such reason. Appellants assert that such a suggestion or motivation to combine or modify the teachings of the cited references cannot be found in the knowledge of one having ordinary skill in the art. However, the rejection has in fact provided a clear rationale for combining all of these references. All 5 references are clearly discussing the production of PHA polymers and thus all relate to the same technology and thus are clearly combinable. Furthermore as discussed above, the rejection clearly sets forth the specific reasons for each of the conclusions made within the instant rejection. However, the Supreme Court in *KSR International Co. v. Teleflex Inc.* (82 USPQ2d 1385, 2007) made it clear that an explicit suggestion to combine references is not necessary. The court clearly stated:

> "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability." (Page 1396)
>
> and

> "Following these principles may be more difficult in other cases than it is here because the claimed subject matter may involve more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement. Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. See *In re Kahn*, 441 F.3d 977, 988 [78 USPQ2d 1329] (CA Fed. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." (Page 1396)

Thus appellants statement that motivation to combine or modify the teachings of the cited references cannot be found in the knowledge of one having ordinary skill in the art has been clearly acknowledged by the Court to be incorrect and the instant rejection clearly sets forth the reasoning and its rational underpinning used to support the legal conclusion of obviousness. For all the reasons discussed above, the rejection is maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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